patients find such simple measures to be frequently if not universally successful.

The suggested use of antiandrogens and metabolic inhibitors to reduce sebum production is another matter altogether. For one thing, it has never been demonstrated that the oiliest areas of the face get the most acne. The lesions of acne do not occur in those sites where sebum flow is most profuse but only in those areas where the outflow of sebum to the surface is blocked. The validity of this statement may be confirmed if one will look carefully at any random group of acne patients.

The largest and most productive sebaceous glands are on the nose, yet pimples on the nose are characteristic only of very early adolescence, at a time when the remainder of the sebaceous follicles on the face are still quite inactive. As follicular development continues, sebum and pimples start to appear on the central portion of the cheeks; later they appear on the outer parts of the face and finally on the neck and back. Of particular interest is the fact that at the same time as the sides of the face become affected it is customary for the nose and central cheeks to become relatively free of lesions. Careful examination of such patients reveals that the nose and central cheeks are quite oily and shiny. They are free of active disease not because the production of sebum has lessened in those areas but because the follicles, now mature, have at last become capable of emptying themselves through adequate openings. This, in fact, is how one literally "outgrows" acne. The openings become enough to function while sebum production continues at a normal and natural rate.

Thus the suggested treatment of acne with antiandrogens and antimetabolites in addition to being potentially harmful through effects elsewhere in the body, is also not "rational." —I am, etc.,

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1 Cunliffe, W. J., and Shuster, S., *Lancet*, 1969, **1**, 685.

Vehicles for the Disabled

SIR,—As a general practitioner with several handicapped patients I would like to express my deep concern about the highly unsatisfactory invalid three-wheelers issued to the disabled by the Department of Health and Social Security. These have attracted widespread criticism in recent years, and when compared with an adapted four-wheeled car (which is comparable in cost to a three-wheeler) in the August 1969 edition of *Which?* they were described as "underpowered, unstable, unreliable, . . ., noisy, poorly heated, and did not ride very well."[1] They were summed up as "fairly disastrous" vehicles. To answer such criticisms a new three-wheeler—the P.70—was introduced in 1970. While improved features included a more powerful engine and automatic transmission, the light fibreglass body and inherently unstable concept of three wheels instead of four remained the same. This "improved" model was strongly criticized in a further *Which?* report in March 1972[2] and summed up as "still extremely hazardous" owing to lack of safety features.

Having personally tested the new P.70 three-wheeler, I found that the comments made in *Which?* and the frequent complaints of local disabled drivers about the instability of such vehicles and their proneness to being blown around in cross-winds were more than fully justified. In recent years three disabled drivers have been blown off the road in the Oxford area alone (one of whom was killed) and one of my patients recently suffered the same misfortune in the new P.70 three-wheeler, but luckily escaped alive.

It is to be hoped that more individual doctors, and the medical profession as a whole, will soon take a more active interest in supporting a call for urgent action to replace existing three-wheelers (except to the minority who cannot drive anything else) with an adapted four-wheeled car which is efficient and able to meet the safety standards of the twentieth century—a concession already enjoyed by war disabled persons and some categories of National Health Service patients. Any doctor who doubts the need for such proposals has only to inspect the controls and test-drive (not on a public road) any three-wheeler issued to his disabled patients by the Department of Health, and compare it with an automatic Mini-minor or similar small car for comfort, ease of control, and particularly safety, to realize the validity of the criticisms of such vehicles. Haematologists have already been strongly outspoken in successfully drawing attention to the dangers of three-wheelers for severe sufferers from haemophilia. Perhaps other doctors should show similar concern and adopt a similarly urgent course of action on behalf of their severely disabled patients.

I would be interested to hear from any doctor who has views on this subject and who would be willing to take an interest in support of trying to achieve safer vehicles for disabled drivers.—I am, etc.,

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1 *Which?*, August 1969, p. 248.
2 *Which?*, March 1972, p. 94.

Bone Marrow in Infectious Mononucleosis

SIR,—Your leading article, "Infection with E.B. Virus" (31 March, p, 757), contains the statement that "infectious mononucleosis does not involve the bone marrow." We wish to draw attention not only to our own series of nine patients,[1] but also to a pre-existing literature on this topic.

In our series, all specimens of sternal marrow showed marked hyperplasia affecting all cellular elements, and very occasionally the cellular features could be so bizarre as to raise the possibility of an early neoplastic process affecting one or more cell lines. From the literature we select the articles by Campbell,[2] Schleicher,[3] Hovde and Sundberg,[4] and Pease,[5] all of whom noted involvement of the marrow either by hyperplasia or by granulomata or by both features in most of the patients studied. Further, since our own publication, Metcalf and Wahren[6] have reported the presence in the serum of 44-100% of patients with infectious mononucleosis of a factor which possesses colony-stimulating activity on mouse bone marrow cells in vitro.

Hence all these reports lead us to conclude that infectious mononucleosis does indeed affect the marrow in a very interesting manner and that there can be from time to time close similarities between the marrow findings in infectious mononucleosis and other generalized lymphoproliferative states.—We are, etc.,

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1 Boyd, J. F., and Reid, D., *Journal of Clinical Pathology*, 1968, **21**, 683.
2 Campbell, A. C. P., *Journal of Pathology and Bacteriology*, 1948, **60**, 629.
3 Schleicher, E. M., *Acta Haematologica (Basal)*, 1949, **2**, 242.
4 Hovde, R. F., and Sundberg, R. D., *Blood*, 1950, **5**, 209.
5 Pease, G. L., *Blood*, 1956, **11**, 720.
6 Metcalf, D., and Wahren, B., *British Medical Journal*, 1968, **2**, 99.

Strychnine-containing Tonics

SIR,—Along with two colleagues we recorded, in 1971, the successful treatment of strychnine poisoning with diazepam.[1] The patient, a 13-month-old child, had accidentally swallowed Easton's tablets (formula A, *B.P.C.* 1963). These are a "tonic" and at the time contained 1 mg of st. chnine hydrochloride per tablet.[2] We conde.. e use of strychnine in any form because t.. is no evidence of any therapeutic value. Tolerance to strychnine is variable and as little as 2 mg has proved unpleasant to adults[3]; no one knows the effect a lower dose may have on children, but it might be fatal. In the 1968 revision of the *B.P.C.* the strychnine content of the formula A tablet was reduced to 0·1 mg, but the preparation was not withdrawn altogether, apparently because there was still a demand for it; the tablets are still being manufactured.

As no one knows the lowest fatal dose of strychnine in children, and as strychnine has no therapeutic indications, it seems improper to continue to produce any compound with any form of strychnine as its ingredient. Many "tonics" taste very pleasant, which makes them especially attractive to children.[4]

A brief scan of *MIMS* has shown that there are at least nine proprietary preparations still marketed as "tonics" which contain strychnine in various forms and in varying (sometimes unspecified) dosage. There may well be others, and we should therefore like to ask these questions: (1) As strychnine has no proved clinical value and is a known poison, does commercial success in so-called "tonic" sales outweigh the risk of unnecessary fatalities? (2) What company can justify the continuing manufacture of preparations containing this ingredient? (3) When are the drug companies going to withdraw these compounds in their present form? (4) Should not the Committee on Safety of Medicines be involved?

In the meantime we appeal to all doctors not to prescribe any of these so-called "tonics" and to try to retrieve any which may be in the possession of patients. Most patients are surely unaware that the tonic

they use could kill their children.—We are, etc.,

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1 Jackson, G., Ng, S. H., Diggle, G. E., and Bourke, I. G., *British Medical Journal*, 1971, 3, 519.
2 Martindale, W., *The Extra Pharmacopoeia*, ed. R. G. Todd, 25th edn. London, Pharmaceutical Press. 1967.
3 Thienes, C. H., and Haley, T. J., *Clinical Toxicology*, 4th ed. London, Kimpton, 1964.
4 Southby, R., *Medical Journal of Australia*, 1965, 1, 533.

Camphor Poisoning in Children

SIR,—I should like to support Dr. J. R. Sibert's comments on camphor poisoning in children (31 March, p. 803). Our experience with this substance at this hospital is in fact less than that in Newcastle, amounting to only two cases out of a total of 260 children admitted after ingesting various kinds of poison over the same period as that reviewed by Dr. Sibert (1970-2). This year, however, up to the end of March we have so far admitted two children who had ingested camphorated oil out of a total of 34 cases.

As pointed out by Dr. Sibert, camphorated oil is said to be lethally dangerous, fatalities having occurred after swallowing one teaspoonful. It seems incredible to me that such a substance should be so freely available to the public; and neither can one blame parents for taking few precautions to prevent its being handled by children when it is often sold specifically for rubbing into babies' chests and has even been smeared on their lips to prevent chapping. Surely it would not be too difficult to prevent the sale over the counter of this substance, which is both highly dangerous and of doubtful medical value.—I am, etc.,

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Duration of Action of Beta-blocking Drugs

SIR,—The observations of Drs. P. D. Nigam and A. S. Malhotra (24 March, p. 742) on the prolonged action of pindolol in the management of angina pectoris are of great interest.

Despite their established place and wide use in clinical medicine, little information is available about the duration of action of beta-adrenergic blocking drugs. Propranolol has been shown to have a pharmacological half-life of 11 hours as judged by inhibition of an isoprenaline tachycardia[1] and, although the plasma half-life of practolol is reported as 10 hours,[2] its pharmacological half-life has not been determined. Recently 5 mg of pindolol given orally has been shown to act for significantly longer than 100 mg of propranolol.[3] Knowledge of the duration of action is of vital importance in determining the dose frequency and effectiveness of any drug.

We have recently carried out observations on the duration of action of several beta-blocking drugs in normal volunteers using a standardized exercise test to produce a marked increase in heart rate as a result of increased sympathetic stimulation of the heart. Exercise was performed before and at intervals after the oral administration of alprenolol, sotalol, and practolol. The effect of each drug has been presented as a percentage reduction in the exercise tachycardia present before drug administration (table I). In the subjects who received practolol plasma levels and urinary excretion of the drug were determined.

TABLE I—*Effect of Beta-blocking Drugs on Exercise Tachycardia*

Drug	Dose (mg)	No. of Subjects	Reduction in Exercise Tacyhcardia (%)						
			2-3 hr	7-8 hr	24 hr	36 hr	48 hr	72 hr	96 hr
Placebo ..		6	0	0	0	—	0	0	—
Alprenolol ..	100	3	16·4	8·0	0	—	—	—	—
Alprenolol ..	400	3	26·8	25·0	10·1	7·4	—	—	—
Sotalol ..	100	3	16·1	13·8	10·6	—	—	—	—
Sotalol ..	400	3	27·4	24·8	23·4	17·2	23·1	6·5	11·8
Practolol ..	100	3	23·1	—	13·5	—	—	—	—
Practolol ..	200	3	26·4	—	19·1	—	—	—	—
Practolol ..	400	6	25·7	24·3	21·7	—	14·5	9·9	2·3
Practolol ..	800	3	27·5	—	22·1	—	—	—	—

TABLE II—*Relation of Reduction in Exercise Tachycardia to Blood Practolol Level*

	0 hr	3 hr	7 hr	24 hr	48 hr	72 hr	96 hr
Reduction in exercise tachycardia (%) ..	0	25·7	24·3	21·7	14·5	9·9	2·3
Blood practolol level (μg/ml)	0	3·5	3·1	1·2	0·45	0·15	0

Several conclusions may be drawn from these results. Firstly, maximum blockade of an exercise tachycardia was not produced by 100 mg of alprenolol or sotalol but was produced by this dose of practolol. Secondly, alprenolol, sotalol, and practolol in doses of 400 mg were equally effective initially, but sotalol and practolol continued to produce blockade of 20% or greater at 24 hours, at which time the effect of alprenolol had diminished to 10%. This dose of sotalol and practolol had some effect on an exercise tachycardia for up to 72-96 hours. This effect did not result from the subject becoming accustomed to the repeated periods of exercise as there was no change in an exercise tachycardia after administration of a placebo. Thirdly, increasing the dose of practolol from 100 to 800 mg did not produce greater maximum reduction in the exercise tachycardia, but it did increase the duration of effective blockade.

Values for the percentage reduction in an exercise tachycardia and the blood practolol levels in six subjects given 400 mg of practolol orally are shown in table II. It will be seen that the decay of the blockade curve appears to be less rapid than that of the blood practolol level. Thus although the plasma half-life of practolol is about 10-11 hours, the pharmacological half-life appears to be of the order of 40-50 hours. As all but 10-30 mg of this dose of practolol had been excreted in the urine in the first 48 hours, it would appear that it may be bound to the tissues, and that this accounts, at least partially, for the long duration of action.

These results, together with those of other studies currently in progress in this department, indicate that the maximum reduction of an exercise tachycardia produced in normal subjects with practolol given either orally or parenterally depends upon the achievement of a blood practolol level of 1·0 μg/ml. As long as the blood practolol level is maintained above this value, an exercise tachycardia will be reduced by at least 20%. It is shown in table II that, on this basis, an oral dose of 400 mg of practolol need only be taken once daily; we would predict from studies at present in progress that 800 mg of practolol would be effective for 48 hours, as the blood practolol level is about 3·0 μg/ml 24 hours after such a dose.

The prolonged effect of pindolol observed by Drs. Nigam and Malhotra may also be explained on this basis. A 10-mg dose of pindolol maintains complete blockade at 24 hours[4] and has been shown to be about 40 times more active than propranolol in inhibiting an isoprenaline tachycardia.[3] Therefore the dose of pindolol (5 mg four times daily) had about five times the activity of the dose of propranolol (40 mg four times daily) and in addition was about twice the dose required for a maximum effect. It is possible that after four weeks on such a regimen blood levels of pindolol had been achieved in excess of those required and may have been maintained for much of the first week after cessation of therapy above the level required for a blocking effect.

Little attention has been focused on this important area of the clinical pharmacology of beta-blocking drugs. Studies on these drugs have often been terminated within eight hours, thus failing to obtain much vital information. It is our contention that rationalization of dosage regimens is long overdue, even with drugs like propranolol and practolol which have now been in clinical use for more than five years.—We are, etc.,

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1 Paterson, J. W., Conolly, M. E., Dollery, C. T., Hayes, A., and Cooper, R. G., *Pharmacologia Clinica*, 1970, 2, 127.
2 Fitzgerald, J. D., and Scales, B., *International Journal of Clinical Pharmacology, Therapy and Toxicology*, 1968, 1, 467.
3 Aellig, W. H., *British Journal of Pharmacology*. In press.
4 Olsson, S. B., and Varnauskas, E., *Indian Heart Journal*, 1972, 24 (Suppl. 1), 167.

Biological Availability of Digoxin

SIR,—The comparative study of "new" and "old" Lanoxin by Dr. D. Falch and others (24 March, p. 695) seems to perpetuate some misconceptions with regard to the significance of plasma levels of dixogin.

The action of digoxin is not closely related to the plasma level but depends on the relatively slow uptake of the drug on the active